REMARKS

Reconsideration of the rejections set forth in the Office action mailed January 24, 2003 is respectfully requested, for the reasons discussed below.

I. Amendments

In independent claim 1, the phrase "complementary or near-complementary regions of the probe and at least one such analyte molecule are stably hybridized" is replaced with "the probe forms stable duplexes with a plurality of or all of the analyte molecules", and "separating said species" is amended to "separating said duplexes from each other and from single stranded species". Support is found, for example, at the sentence bridging pages 2-3 of the specification.

In addition, the preamble of claim 1 is amended to recite "separating", rather than "analyzing", a population of analyte molecules, in accordance with the final step of the claim. The preamble is also amended to explicitly recite a population of "different" analyte molecules. Support is found, for example, in original dependent claim 4, which refers to duplexes of the probe "with different analyte molecules".

Claims 12-14 are cancelled to expedite prosecution.

No new matter is added by any of the amendments.

II. The Invention

The applicant's invention, as embodied in independent claim 1, provides a method of separating a population of different oligomeric analyte molecules which are substantially uncharged. Each analyte molecule is able to hybridize with a specific charged probe molecule, which is a nucleic acid or a charged nucleic acid analog. The method comprises the steps of:

(a) applying the analyte molecules and the probe molecule to a charge-bearing separation medium, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded analyte, single stranded probe, and combinations thereof; and

(b) separating the duplexes from each other and from single stranded species within the medium.

Benefits of the Invention

As discussed in the Background of the specification, charge-based separation methods, such as ion exchange chromatography, are widely used for separation of charged oligomers, such as nucleic acids, but they are less useful for separation of substantially uncharged oligomers. Conventional ion exchange separation of oligonucleotide analogs having uncharged linkages generally employs ionization of the base moieties. By carrying out the separation at very high pH (>11), G and T bases ionize, and at very low pH (<3), C and A bases ionize. However, some types of linkages are unstable at these extreme pH levels. (See specification, page 1, lines 18-22. This method of separation is also described in cited reference Summerton *et al.*)

The present method, which can be carried out at neutral or near-neutral pH, employs a specific charged probe molecule, as recited in claim 1, which forms duplexes with some or all of the analyte molecules. Duplexes of different analyte molecules with the same probe molecule will, of course, differ from each other. It is the discovery of the applicants that these duplexes of the different analyte molecules with the charged probe molecule can be separated in a charge-bearing medium, on the basis of differing amounts of unconstrained single stranded probe molecule in the different duplexes. See the discussion at page 9 of the specification, with reference to Figs. 3-4.

Working Examples

To illustrate the method, Example 1 shows separation of duplexes of a probe DNA with several uncharged oligomers which vary in length from 13 to 20 subunits (Example 1, page 15; Figs. 5A-B). Example 2 shows separation of duplexes of a probe DNA with several same-length uncharged oligomers, where the oligomers differ in sequence only by deletion of one nucleotide subunit at various positions (Example 2, page 16; Figs. 6-8).

III. Rejections under 35 U.S.C. §112, Second Paragraph

Independent claim 1 and dependent claims 2-27 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claim 1 was rejected as lacking final process steps that clearly relate back to the

preamble. Accordingly, the preamble has been amended to recite "separating", rather than "analyzing", a population of analyte molecules, in accordance with the final step of the claim.

The term "near" in dependent claim 12 was objected to. Although the applicants believe that the embodiment of dependent claims 12-14 would be clear to one skilled in the art, especially in light of the description in the specification at page 10, lines 19-25, these claims have been cancelled to expedite allowance of the remaining claims.

In view of the foregoing, the applicants submit that the amended claims comply with the requirements of 35 U.S.C. §112, second paragraph.

IV. Rejections under 35 U.S.C. §102(b)

Claims 1-5, 10, 12-13, 15, and 18-27 were rejected under 35 U.S.C. §102(b) as being anticipated by Summerton *et al.*, U.S. Patent No. 5,034,506. This rejection is respectfully traversed for the following reasons.

The standard for lack of novelty, that is, for anticipation, is one of strict identity. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986); *In re Donohue*, 766 F2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985). To anticipate a claim for a patent, a single prior source must contain all its essential elements.

A. The Invention

The applicant's invention, as embodied in independent claim 1, provides a method of separating a population of different oligomeric analyte molecules which are substantially uncharged. Each analyte molecule is able to hybridize with a specific charged probe molecule, which is a nucleic acid or a charged nucleic acid analog. As described above, the method comprises the steps of:

(**a**) applying the population of analyte molecules and the probe molecule to a charge-bearing separation medium, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded analyte, single stranded probe, and combinations thereof; and

(**b**) separating the duplexes from each other and from single stranded species within the medium.

B. The Prior Art

The cited reference, U.S. Patent No. 5,034,506, and in particular the sections pointed out by the Examiner, describe conventional methods of analyzing or purifying uncharged morpholino-based oligomers.

For example, at column 33, lines 22-29, column 34, lines 22-49, and column 35, lines 41-49,[1] the '506 patent describes methods for testing the binding of such an oligomer to "its complementary DNA" (column 33, line 24). This is done by "monitoring the absorbance in the 240 to 290 nm wavelength region" of a mixture of these two compounds, which is a conventional procedure for determining the Tm (melting temperature) of a duplex (see column 35, line 45). As further described at column 34, lines 45-69, this monitoring is carried out in solution in a spectrometer. There is no disclosure of "applying a population of different analyte molecules and the probe molecule to a charge-bearing separation medium".

The Examiner also points out sections of the reference[2] which describe conventional ion exchange purification of the uncharged oligomers, carried out at low pH (2.5) or high pH (11), as noted in the Background of the applicant's specification. There is no indication in the reference that any "probe molecule", consisting of a "nucleic acid or a charged nucleic acid analog", as recited in claim 1, is present during these ion exchange procedures.

In view of the above, the reference does not disclose "applying the analyte molecules (i.e., a "population of different oligomeric analyte molecules") and the probe molecule to a "charge-bearing separation medium", as recited in step (**a**) of claim 1.

Nor does the reference disclose separating, within a charged medium, probe-analyte duplexes from each other, as recited in step (**b**) of claim 1.

Since the reference does not disclose all of the elements set out above in independent claim 1, and present in dependent claims 2-27, the claims are not anticipated by this reference. The applicant therefore respectfully requests the Examiner to withdraw the rejection under 35 U.S.C. §102(b).

[1] Cited in the 1st, 2nd, 3rd and 5th paragraphs on page 4, the 1st and 2nd paragraphs on page 5, and the 2nd and 3rd paragraphs on page 6 of the Office Action

V. Rejections under 35 U.S.C. §103

Claim 6 was rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.* (U.S. Patent No. 5,034,506). Other rejections under this section were made as follows:

Claims 1-13, 15, and 18-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Connolly *et al.* (U.S. Patent No. 6,342,370).

Claims 1-6, 10, 12-16, and 18-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Gilmanshin *et al.* (U.S. Patent No. 6,263,286).

Claims 1-6, 10, and 12-27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Gilmanshin *et al.*, above, and further in view of Hearn *et al.* (U.S. Patent No. 4,279,724).

The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, and the benefits thereof, are discussed above in Section II.

B. The Cited Art

The primary cited reference, U.S. Patent No. 5,034,506, as discussed above, describes conventional methods of analyzing or purifying uncharged morpholino-based oligomers. These include ion exchange purification of a morpholino oligomer, at high (11) or low (2.5) pH, from a synthetic reaction mixture (column 32, lines 48-59 and columns 12-13, pointed out by the Examiner). Although the full length oligomer may be separated from "shorter failure sequences" during this purification (column 13, lines 1-2), there is no indication that any charged nucleic acid probe molecule is present during this procedure.

Nor is there any suggestion of any reason one would be motivated to include a charged nucleic acid probe molecule in such a procedure. The Examiner refers to the combination of a single morpholino oligomer with a single DNA molecule, for determination of binding (Tm)[1], but this is in a separate procedure having nothing to do with purification or separation of oligomers. Furthermore, the Tm determination involves a single morpholino oligomer, not a population of different oligomers.

This reference provides no suggestion whatsoever of the method of independent claim 1 and

[2] Columns 32 and 12-13, cited in the 2nd paragraph on page 4 and the 5th paragraph on page 5 of the Office Action.

its advantages over conventional separations of substantially uncharged oligomers. The present invention is based on the discovery that duplexes of the different substantially uncharged analyte molecules with the same charged probe molecule can be separated in a charge-bearing medium. There is no suggestion in the reference to combine a population of different, substantially uncharged analyte molecules with a charged probe molecule, to apply the mixture to a charge bearing medium, and to separate duplexes within the medium.

The secondary references are cited for their disclosure of various individual features of dependent claims 2-27. Briefly, Connolly *et al.* is cited for the disclosure of probes containing deletion variant sequences. In Connolly, these are used for diagnosis of disorders related to mutations in the DNA of an individual (e.g. column 2, lines 46-50).

Gilmanshin *et al.* is cited for the disclosure of fluorescent labeling moieties and the use of electrophoresis. Both of these techniques are of course used in many different technologies, including DNA sequencing. In the sections of this reference pointed out by the Examiner, these techniques are used for labeling of short probes which bind to a DNA to be sequenced, which probes can then be removed by electrophoresis (column 19, lines 14-21); or in FRET analysis (columns 20-26).

Hearn *et al.* is cited for its disclosure of a superimposed pH gradient, for use in "preparative electrofocusing of protein mixtures" (column 1, lines 47-49).

The teachings of these references, directed to various technologies, provide no further guidance regarding a method of separating substantially uncharged oligomeric molecules which form duplexes with a charged probe molecule. Even if the teachings of the secondary references were combined with that of Summerton *et al.*, these combined teachings would not suggest the claimed method.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

VI. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

Date: 4-24-03

LeeAnn Gorthey
Registration No. 37,337

Correspondence Address:
PAYOR NUMBER 22918
PHONE: (650) 838-4403
Fax: (650) 838-4350